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Copper(II)-Catalyzed Enantioselective Intramolecular Carboamination of Alkenes

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The transition-metal mediated intramolecular carboamination of alkenes is a direct method for complex nitrogen heterocycle synthesis. A number of research groups have investigated this transformation in recent years.[1] The catalytic asymmetric carboamination of alkenes is an obvious challenge for these reactions, and has been realized rarely.[1d] Herein is described a novel copper(II)-catalyzed asymmetric carboamination reaction that involves intramolecular addition of arylsulfonamides across terminal alkenes to provide chiral sultams. Sultams and sulfonamides are common components of biologically active small molecules.[2]

The copper-facilitated synthesis of heterocycles via addition of heteroatoms to alkenes and alkynes is an important area in organic synthesis.[3] We have recently reported the first copper (II)-facilitated intramolecular carboamination of alkenes, a net oxidative cyclization process (Scheme 1).[1c,f] In depth mechanistic studies led us to conclude that the stereochemistry determining C-N bond forming step occurred via syn aminocupration of the alkene (cf. **3** → **5** via **4**, Scheme 1).[1f] If the copper salt is involved in the stereochemistry-determining step, chiral ligands on copper could allow for a stereocontrolled synthesis of the product. In the proposed C-N bond-forming transition state **4**, the substrate occupies two coordination sites on a tetracoordinate copper(II),[4] leaving two coordination sites available for a bidentate ligand (Scheme 1). Inspired by this analysis, we initiated a search for an appropriate oxidant for copper turnover and ligand for asymmetric induction. Herein is reported the first catalytic as well as catalytic asymmetric variant of this copper(II)-facilitated carboamination reaction.

In the search for conditions catalytic in copper, we screened a number of oxidants [O_2, PhI$(OAc)_2$, oxone, Me_3NO, MnO_2],with and without ligands in different solvents for the conversion of **1a** to **2a** with a catalytic amount (0.2 equiv) of copper(II) ethylhexanoate. The highest conversions were obtained with MnO_2 (3 equiv) as oxidant in trifluorotoluene in the presence of ligands (Table 1). Under the optimized conditions but in the absence of copper(II), no reaction occurs. In toluene, a mixture of carboamination and hydroamination products **2a** and **7** was observed (Table 1, entries 3 and 4). We hypothesized the hydroamination product **7** is formed via carbon radical (e.g. **6**) capture of a hydrogen atom from solvent. Gratifyingly, changing the solvent to trifluorotoluene substantially decreased formation of the hydroamination adduct (Table 1, entries 5, 6 and 8). The carboamination reactions stoichiometric in copper(II) (cf. Scheme 1) start out blue [due to copper(II)] and terminate as orange-brown heterogeneous mixtures, indicating formation of copper(0), possibly from disproportionation of copper(I) to copper(II) and copper(0). Reoxidation of copper(0) under the mildly basic reaction conditions used in these reactions is challenging. We hypothesized that ligands would stabilize copper(I) and copper(II) in preference to copper(0).[3] Addition of diethylsalicylamide **8** (0.2 and 0.8 equiv) increased the reaction yields, likely due to improved copper turnover (Table 1, compare entries 1 and 2 with 3–6).[5] We changed the copper(II)

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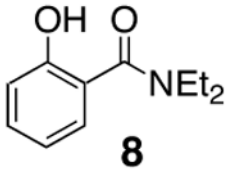
source to $Cu(OTf)_2$ to achieve better ligand chelation (entries 6–8). The bipyridine ligand **9** (0.2 equiv) gave more efficient conversion when $Cu(OTf)_2$ was used (compare entry 6 to 8).



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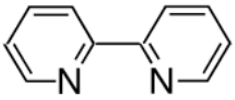

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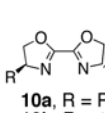
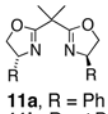
We screened chiral ligands **10–13** by precomplexing $Cu(OTf)_2$ (0.2 equiv) with ligand (0.2 equiv) followed by addition of substrate **1a**, K_2CO_3 (1 equiv) and MnO_2 (3 equiv) and heating in a sealed tube for 24 h in $PhCF_3$ (Table 2).

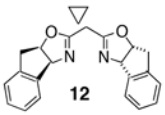
We quickly found that 2,2-bis[(4*R*)-4-phenyl-2-oxazolin-2-yl]propane (**11a**) gave the highest asymmetric induction, providing carboamination adduct **2a** in 85% isolated yield, 92% enantiomeric excess (Table 2, entry 5). We were unable to reduce the catalyst loading below 0.2 equiv without adversely affecting the product yield (Table 2, entries 10 and 11). Lowering the reaction temperature to 110 °C provided the product in slightly lower yield (72%) and 94% enantiomeric excess (Table 2, entry 12). Ligands **12** and **13** rendered the copper(II) complex less reactive (entries 8 and 9).



10a, R = Ph
10b, R = *t*-Bu
10c, R = Bn



11a, R = Ph
11b, R = *t*-Bu
11c, R = Bn



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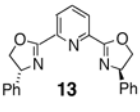

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The generality of the reaction was examined as shown in Table 3. γ-Alkenyl arylsulfonamides **1** cyclized in 45–85% yield and 80–94% ee.[6] The 2-sulfamido thiophene substrate **1 4** reacted very sluggishly but with good enantioselectivity. *N*-Tosyl-2-allylaniline **16** reacted efficiently but with low (46%) enantioselectivity and *N*-tosyl-2-allylbenzylamine **18** reacted sluggishly and in moderate yield and enantioselectivity to provide tetrahydroisoquinoline **19** (entry 12).

X-Ray crystal structures of sultams **2g** and **15** indicate the (*S*)-configuration. The other carboamination adducts in Table 3 are assigned the S stereochemistry by analogy. Sultam **2i** was converted to the known 2(*S*)-benzylpyrrolidine **20,**[7] an intermediate used in the synthesis of a potent calcium-sensing receptor antagonist,[8] by reductive removal of SO_2 (Scheme 2). Pyrrolidine (*S*)-**20** is thus available by this method in three steps from commercially available starting materials (see Supporting Information for complete details).

The observed stereochemistry is consistant with transition state **A** (Scheme 2), where the substrate's *N*-substituent is on the face opposite of the oxazoline phenyl substituent it is cis to about the distorted square planar copper center.[4]

The method reported herein provides access to enantiomerically enriched nitrogen heterocycles. Applications of this reaction toward the synthesis of bioactive compounds are underway. This method will also inspire the development of other copper(II)-catalyzed enantioselective amination reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

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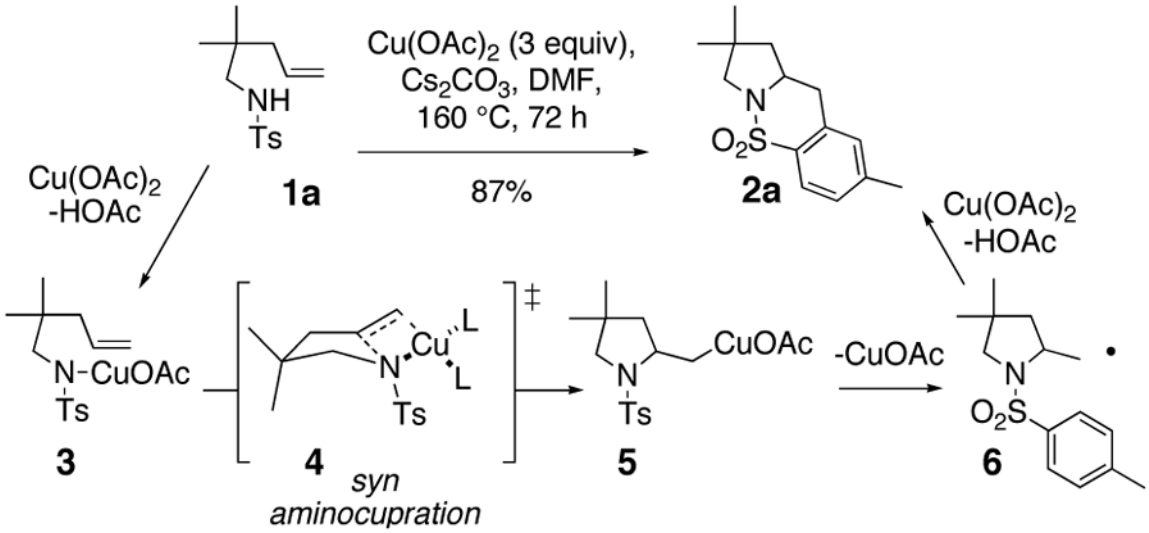
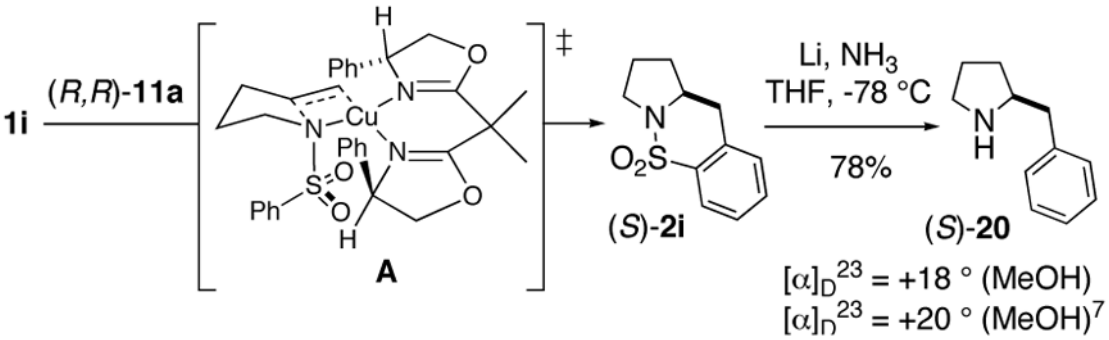


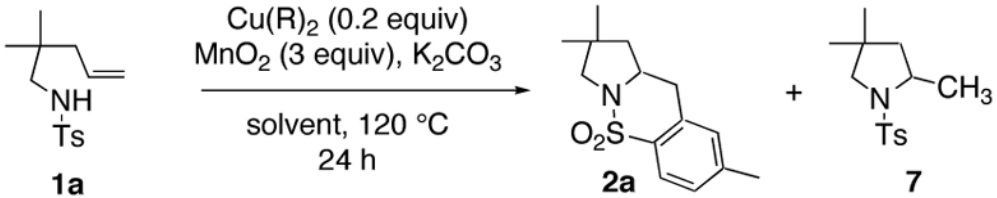
Scheme 1.
Copper(II)-Promoted Carboamination and Mechanism



Scheme 2.
Transition State Model and Removal of SO_2

Table 1

Dependence on Solvent and Ligand[a]



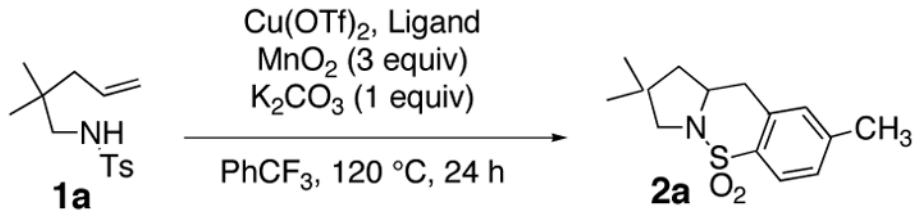
entry	R	solvent	ligand (equiv)	yield (%) 2	yield (%) 7
1	EH	$PhCH_3$	--	<5	trace
2	EH	$PhCF_3$	--	7	trace
3	EH	$PhCH_3$	**8** (0.2)	41	7
4	EH	$PhCH_3$	**8** (0.8)	63	17
5	EH	$PhCF_3$	**8** (0.8)	75	<5
6	OTf	$PhCF_3$	**8** (0.8)	29	<5
7	OTf	$PhCH_3$	**9** (0.2)	59	12
8	OTf	$PhCF_3$	**9** (0.2)	60	<5

[a] Reaction conditions: Substrate **1a** was dissolved in solvent (0.1 M) and treated with K_2CO_3 (1 equiv), MnO_2 (3 equiv), CuR_2 (0.2 equiv) and the specified amount of ligand and stirred in a sealed tube at 120 °C for 24 h.

[b] Yields refer to amount of compound isolated after chromatography on SiO_2. Remainder of material was always unreacted starting **1a.** EH = 2-ethylhexanoate.

Table 2

Chiral Ligand Screening[a]



entry	equiv $Cu(OTf)_2$	ligand (equiv)	yield (%)	%ee[c]	ER[c]
1	0.2	(*R*,*R*)-**10a** (0.2)	54	24	62:38
2	0.2	(*S*,*S*)-**10b** (0.2)	53	14	43:57
3	0.2	(*S*,*S*)-**10c** (0.2)	73	28	36:64
4	0.2	(*S*,*S*)-**11a** (0.2)	75	86	7:93
5	0.2	(*R*,*R*)-**11a** (0.2)	85	92	96:4
6	0.2	(*S*,*S*)-**11b** (0.2)	50	24	38:62
7	0.2	(*R*,*R*)-**11c** (0.2)	55	82	91:9
8	0.2	(*R*,*S*)-**12** (0.2)	<5	--	--
9	0.2	(*R*,*R*)-**13** (0.2)	18	4	48:52
10	0.15	(*R*,*R*)-**11a** (0.15)	64	92	96:4
11	0.05	(*R*,*R*)-**11a** (0.05)	34	--	--
12[d]	0.2	(*R*,*R*)-**11a** (0.2)	72	94	97:3

[a] Reaction conditions: $Cu(OTf)_2$ and ligand were combined, dissolved in $PhCF_3$ (0.1 M w/r to **1a**) and heated at 50 °C for 1 h. Substrate **1a**, MnO_2 (3 equiv) and K_2CO_3 (1 equiv) were added and the reaction tube sealed and heated at 120 °C for 24 h unless otherwise noted.

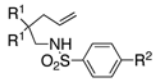
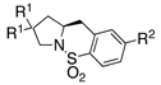
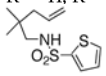
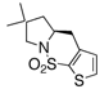
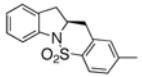
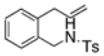
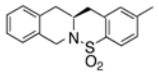
[b] Yield refers to amount of isolated **2a** after purification by flash chromatography on SiO2.

[c] Enantiomeric excess and ratios were determined by chiral HPLC analysis (chiralcel OD-H).

[d] Reaction was run at 110 °C.

Table 3

Scope of Enantioselective Carboamination with (*R*,*R*)-**11a**[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]	ER[c]
					
1	**1a**, R^1 = Me, R^2 = Me	**2a**	85	92	96:4
2	**1b**, R^1= Me, R^2 = H	**2b**	73	92	96:4
3	**1c**, R^1= Me, R^2 = Cl	**2c**	45	92	96:4
4	**1d**, R^1= Me, R^2 = OMe	**2d**	75	94	97:3
5	**1e**, R^1= Ph, R^2 = Me	**2e**	78	94	97:3
6	**1f**, R^1 = -$CH_2(CH_2)_2CH_2$-, R^2= Me	**2f**	83	92	96:4
7	**1g**, R^1= -$CH_2(CH_2)_3CH_2$-, R^2 = Me	**2g**	68	92	96:4
8	**1h**, R^1= H, R^2 = Me	**2h**	68	80	90:10
9	**1i**, R^1 = H, R^2= H	**2i**	77	82	91:9
10[d]	 **14**	 **15**	30	86	93:7
11	 **16**	 **17**	75	46	73:27
12[d]	 **18**	 **19**	63	72	86:14

[a]Reaction conditions: $Cu(OTf)_2$ (0.2 equiv) and (*R*,*R*)-**11a** (0.2 equiv) were combined and treated with $PhCF_3$ (0.1 M w/r to substrate) and heated at 50 °C for 1h. Substrate (1 equiv), MnO_2 (3 equiv) and K_2CO_3 (1 equiv) were added and the reaction tube was sealed and heated at 120 °C for 24 h unless otherwise noted. All reactions were run at least two times to ensure reproducibility.

[b]Yields refer to amount isolated after purification by flash chromatography on SiO_2.

[c]Enantiomeric excess and ratios were determined by chiral HPLC anlaysis (chiralcel OD-H or AD-RH).

[d]Reactions were run for 96 h.